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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006 and 30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,10-13,17 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,10-13,17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/18/2006 has been entered.

The amendments to the claims have been entered. Claims 1-2, 4, 10-13, 17 and 22 are pending. Claims 3, 5-9, 14-15, 18-21 and 24-49 have been canceled and claims 1, 4 and 22 are amended. Claims 1-2, 4, 10-13, 17 and 22 are currently under consideration.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 16, lines 283, page 52, line 6. Appropriate correction is required

Claim Rejections - 35 USC § 112

The rejection of claims 1, 2, 4,10-13, 17 and 22 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of applicants amendment of claim 1 so as to remove the new matter.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1,2,4,8,10-17, 22 and 24 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the claims.

Claim Rejections - 35 USC § 112

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitation... "TCR-$\alpha\beta^{+}CD4^{+}CD8^{+}$ double positive T-cell .." (claim 22) is considered new matter. Applicants have not indicated where in the specification implicit or explicit support for this limitation can be found. Based on the disclosure as filed a practitioner in the art would not be able to

determine that the inventors contemplated the limitation of "TCR-$\alpha\beta^+CD4^+CD8^+$ double positive T-cell". Further, a key word search of the specification fails to find disclosure of these limitations anywhere in the specification as initially filed. Therefore, since the specification as filed doe not contain support for the term "TCR-$\alpha\beta^+CD4^+CD8^+$ double positive T-cell" it is considered to be new matter. See M.P.E.P. 608.04(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13, 17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims embrace a method of forming cells of T cells linage comprising culturing stem cell or progenitor cells that <u>are capable of</u> differentiating into cells of T cell linage.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 11 11 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v.*

Mahurkar, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification has provided the description of cells capable of differentiation into cells of the T cell lineage" refers hematopoietic progenitor and stem cells and embryonic stem cells that differentiate into cells of the T cell lineage when cultured with a Notch ligand. In addition, specification also contemplates cells capable of differentiation into cells of the T cell lineage may be genetically modified (transduced or transfected) either in nature or by genetic engineering techniques *in vivo* or *in vitro* (see para. 95 of the published application). However, the specification fails to describe cells that are capable to differentiate into T cells upon transfection or transduction with gene, that are capable of performing contemplated biological activity fall into the genus. The specification fails to disclose method for of forming cells of T cell linage by culturing any genetically modified cell that is capable to differentiate to form mature or any T cell linage. The specification does not provide any structure/function of any transduced or transfected cell that is capable to differentiate into T cells. No identifying characteristics are disclosed. Further without a clear teaching of the essential elements or motifs that are required for transducing cells to enable cell capable of differentiate into T cells lack written description. One cannot describe what one has not conceived. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential structures and function of the genes that are essential for a

genus of cell transfected with genus of gene capable to perform contemplated differentiation of cell. The specification does not discloses the knowledge in the prior art and/or a description as to the availability of a representative number of species of such stem cells or progenitor cells that are capable of differentiating into cells by transfecting with any gene *in vitro* or *in vivo* that must exhibit the disclose biological functions as contemplated by the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or structure, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming an unspecified genus of stem or progenitor cells that capable of differentiation into cells of the T cell lineage and are genetically modified that must possess the biological properties as contemplated by applicant's disclosure without defining what it means will do so does not comply with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of stem or progenitor cells that are genetically modified that must be capable of performing contemplated biological functions, and therefore, conception is not achieved until reduction to practice has

occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1,2,4,8,10-17, 22 and 24 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4,10-13, 17 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite "an *in vitro* system". The metes and bound of a "system" are unclear because system claims are not distinctly product, product by process, or method claims, therefore the interpretation of a "system" can vary considerable. Furthermore, in the instant case, it is not apparent whether an *in vitro* system is a product or product by process or process claims,

particularly since system-comprising cell produces a T cell of a specific or multiple linage. In addition, it is further unclear as to what else comprises in the system comprising cell preparation other than OP9-DL-1. In addition, cell preparation comprising OP9 stromal cell in different growth condition may have variable effects depending on presence and/or absence of cytokine and/or growth factors. It is further unclear since T cell with specific markers set forth in the claim is produced using the method recited in claim 22. The meets and bound of the claimed invention is not clear. Claims 2, 4, 10-13, 17 directly or indirectly depend on claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2,4 and 12-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al (2001, J. Exp. Med. 194:991-1001, IDS), Nakano et al. (1994, Science 265:5175 IDS) and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS).

Jaleco et al. provides guidance on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of human hematopoietic progenitor cells (HPCs) but does not support B cell lymphopoiesis (Abstract). Specifically, Jaleco

et al. teaches that culturing HPCs with mouse S-17 stromal cells that express Delta-1 inhibits B cell differentiation and produces CD3+ CD4+CD8+ T cells (pg. 992, Materials and Methods; pg. 995, Table 1). Abbas et al. teaches that T cells that are CD3+ CD4+CD8+ have inherently undergone TCR V(D)J rearrangement {Abbas et al., (1994) Cellular and Molecular Immunology 2nd ed., 1-457; pg. 176, Fig. 8-5; pg.178 col. 1}. Jaleco et al teaches that transfecting S-17 stromal cells specifically blocks B cell lymphopoiesis (Abstract). Further, Jaleco et al. teaches that the immature T cells were separated from the aggregate population of cells (pg. 995, Table 1). Jaleco et al. does not teach using OP-9 stromal cells or inducing lymphopoiesis in mouse cells.

Nakano et al. supplements the guidance of Jaleco et al. by teaching the use of mouse OP-9 stromal cells (which inherently does not express M-CSF) to generate lymphohematopoietic cells (Abstract). Nakano et al. teaches that it is advantageous to use stromal cells lacking M-CSF when studying lymphopoiesis because the presence of M-CSF can inhibit the differentiation of ES cells to blood cells other than macrophages. However, Nakano et al do not teach transfecting OP-9 cells.

supplements the guidance of Jaleco et al. by teaching an *in vitro* system for studying the differentiation of mature mouse T cells from CD3- CD4-CD8- precursors by culturing them with mouse stromal cells (Abstract; pg. 2750, Materials and Methods). However, Tatsumi et al do not teach culturing OP-9 cells.

Based on the guidance provided by Jaleco et al. on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of HPCs but does not support B cell lymphopoiesis and the teachings of Nakano et al. on the advantages

of using OP-9 cells when studying lymphopoiesis, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Jaleco et al. by replacing the mouse S-17 stromal cells with OP-9 cells. Further it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the assay system of Jaleco et al. with the OP-9 cells of Nakano et al. to study mouse T cell differentiation with the mouse precursor cells using the precursors taught by Tatsumi et al.

A practitioner in the art would be motivated to modify the method of Jaleco et al. with the OP-9 cells of Nakano et al. in order to reduce the number of inhibitory ligands and to optimize T cell induction. Further, the practitioner would be motivated to use this system to study mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced

The person of ordinary skill in the art would have a reasonable expectation of success because the modifying the teachings of Jaleco et al. by replacing the S-17 stromal cells with the OP-9 cells of Nakano et al. would have been a routine modification in the art at the time of filing. Further, the use of mouse hematopoietic precursor cells, such as those taught by Tatsumi et al. instead of human hematopoietic precursors would have been a routine modification in the art at the time of filing.

Response to Arguments

Applicant's arguments filed 10/30/2006 have been fully considered but they are not fully persuasive. Applicant argues Jaleco et al uses progenitor cells but is unable to produce any mature T cell that is reiterated in the review of Lehar. Applicants also argue that Nakano et al does not teach a method to generate mature T cell. Only Tatsumi et al teaches the generation of mature T cell from precursor cell that are neither stem nor progenitor cells. Therefore, none of the cited references was able to achieve the generation of mature T cell using stem or progenitor cell.

In response, it is noted claims 1-2 and 4 are interpreted as product comprising co culture of OP9 cells that have been modified to express DL-1 or DL-4 in presence of any stem or progenitor cells. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Claims 1-2, 4 is interpreted as product claims. Regarding claims 1-2 and 4 the issue is how a person of ordinary skill in the art would be motivated to replace stromal cell disclosed by Jaleco et al with stromal cell such as OP9 expressing DL-1 in presence of progenitor. It is emphasized that product (system) requires only cell preparations comprising culture of two-cell type and any characteristics of resulting co culture will be inherent in the teaching of such co culture. It is again noted that claims are drawn to an *in vitro* system that produces plurality of T cell subtypes, including those taught by Jaleco et al. The practitioner would be motivated to use the OP-9 cells taught by Nakano et al because the presence of M-CSF

can inhibit the differentiation of ES cells to blood cells other than macrophages. It is emphasized that a person of ordinary skill would be motivated to practice the teachings of Jaleco et al to use OP-9 cells, transfected with a vector encoding Delta-1, in order to optimize any form of T cell induction and decrease the production of macrophages. This would be especially relevant when studying mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced. Therefore, Jaleco et al provide guidance to use the system of co culture comprising stromal cell modified to express DL-1 in presence of stromal cell and as stated before, a person of ordinary skill would have been motivated to try other stromal cells from other species to optimize T cell induction and production of macrophage. In doing so, the modified co culture would inherently show different characteristics markers depending on cells and culture condition. Given, the, the product (system) is merely required to comprise OP9 that is modified to express DL-1 and support T cell lymphogenesis of stem cell or progenitor cell. The product (in vitro system) used to generate cells of specific linage disclosed by Jaleco et al, Nakano et al and Tatsumi and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir.

1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Regarding claims 12-13 and 17 it is noted that claims are directed to a method of forming cells of the T-cell linage comprising culturing stem or progenitor cells that are capable of differentiating into cells of the T cell linage with an *in vitro* system of claim 1 to form cells of the T cell linage. It is emphasized that system of claim1 comprises cell preparation comprising OP9 stromal cell expressing DL-1 or DL-4 and stem or progenitor cells. These claims recite a limitation "cells that are capable of differentiating into cells of the T cell linage (emphasis added)". In the instant case, specification defines cells of the T cell lineage to include cells that show at least one phenotypic characteristic of a T cell or a precursor or progenitor thereof that distinguishes the cells including expression of one or more proteins specific for T cells (e.g. CD8), or a physiological, morphological, functional, or immunological feature specific for a T cell. Cells of the T cell lineage may be (a) progenitor or precursor cells committed to the T cell lineage; (b) CD25.+ immature and inactivated T cells (see para 99 of the published specification). Capable to form cells of T cells linage" implies a property, however, the instant claims fail to set forth any specific structural or functional limitation that distinguishes T cells obtained by the method of claims 12-13 and 17 from the cited prior art. Therefore, cells obtained from the practicing the method of cited reference would

meet the claim limitation of forming cell of T cell linage including immature T cells.

Applicants argument of incorporating the limitation of claim 24 into the claim 22 to include a method step to isolate increased number of T cell linage that is increased by at least 10 to 15 fold is persuasive and therefore rejection to claim 24 is withdrawn.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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